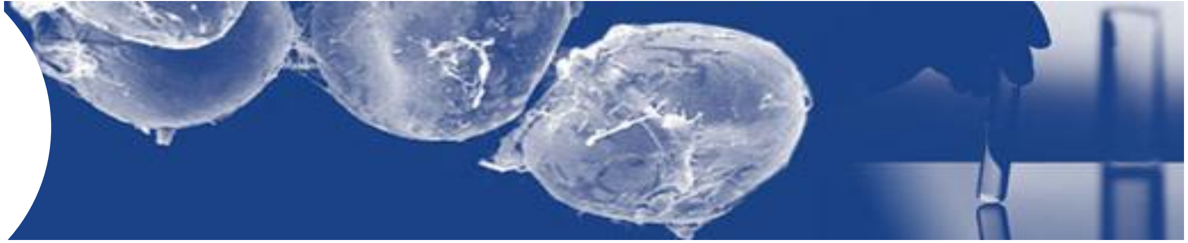

The Way to the Breslow-Intermediate

Seminar talk by
Michael Linden

April 13, **2012**

Institute of Organic Chemistry
Justus-Liebig University Giessen

Outline

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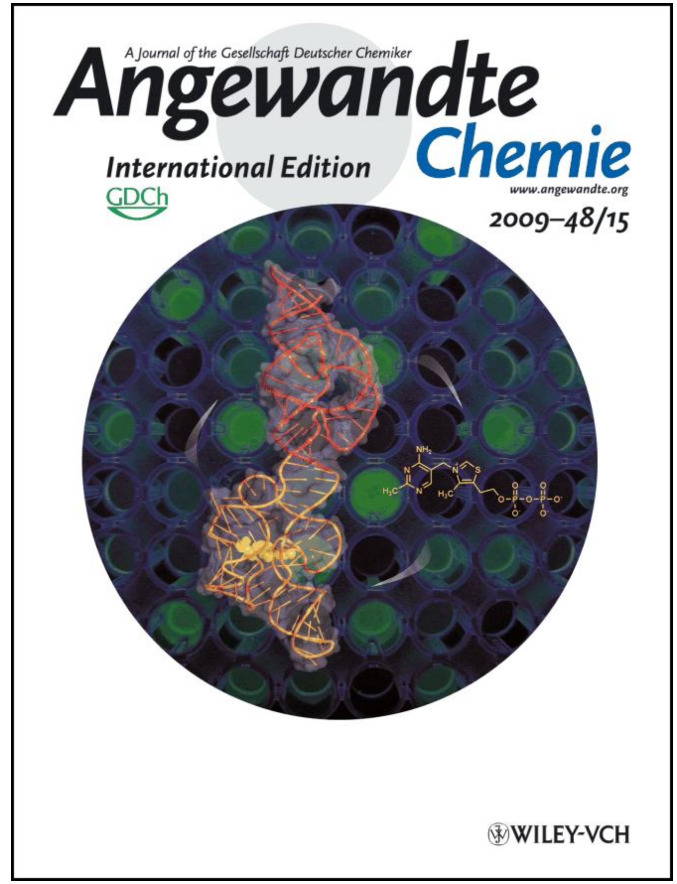
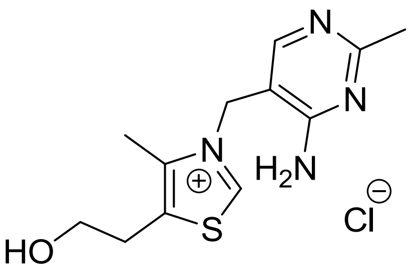
- **Outlook**



Angew. Chem. Int. Ed., **2009**, *15*.

...is a reactive intermediate in thiazolium-catalysed reactions




[a]

- Based on a proposed mechanism by **R. Breslow** in **1958**

  ⮡ similar to the cyanide-catalysed mechanism for *Umpolung* reactions by **A. Lapworth** (**1903**)

advantage : Aliphatic aldehyds can also be used for benzoin-like condensations with thiazolium-salts.

Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995-1005 \ Breslow, R. *J. Am. Chem. Soc.* **1958**, *80* (14), 3719-3726.

Catalytic cycle

e.g., benzoine condensation with thiazolium salt

- Involves a divalent carbon species

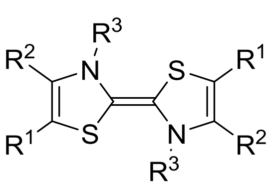
⟶ carbene

- Umpolung reaction

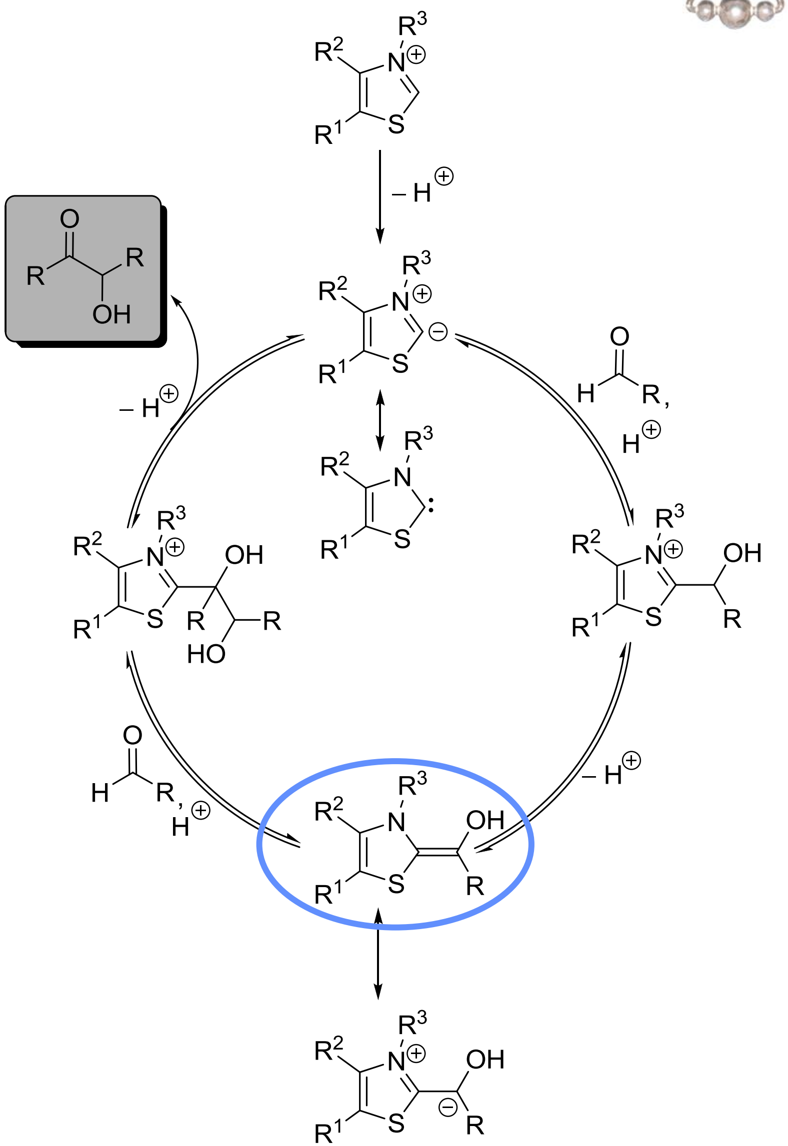
⟶ second attack at aldehyde possible

enaminol = Breslow-Intermediate

- Dimierisation proposed by **D. Lemal** (1964)



bis(thiazoline-2-ylidene)-dimer



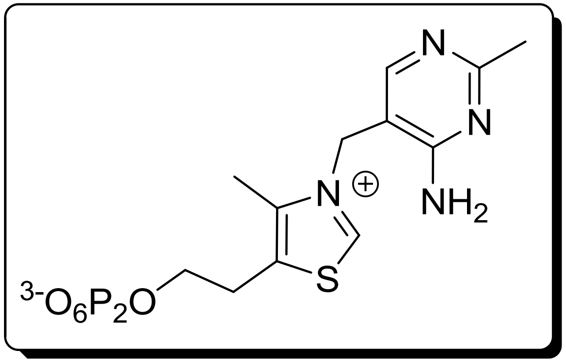
Breslow, R. *J. Am. Chem. Soc.* **1958**, *80* (14), 3719-3726. \ Lemal, D. M.; Lovald, R. A. *J. Am. Chem. Soc.* **1964**, *86*, 2518.

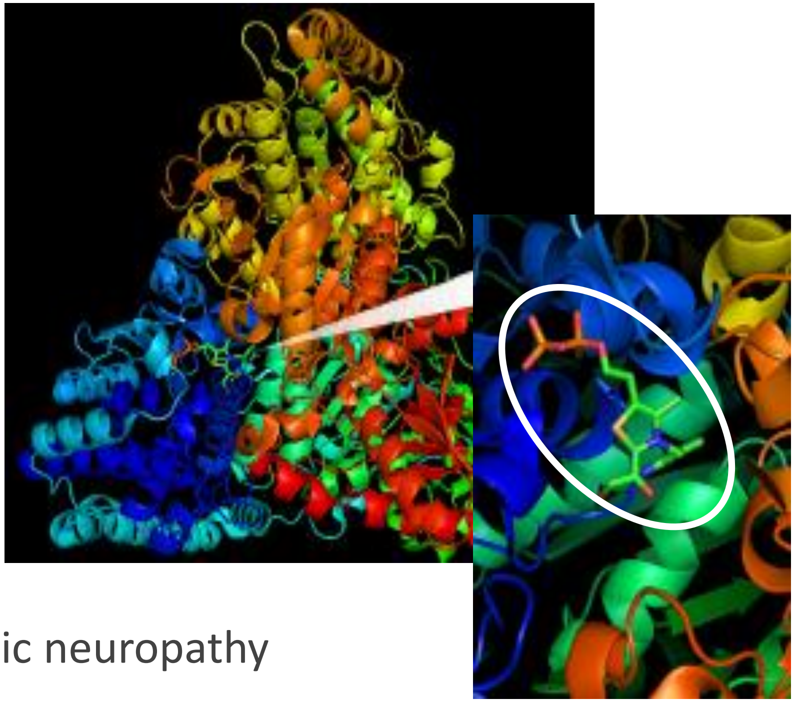
Appearance & relevance

Nature:

- Essential **Vitamin B_1**, which is necessary for many enzymes and catabolic or anabolic biochemical pathways
- Citric acid cycle, pentose phosphate pathway, fermentation (yeast)

Active coenzyme form (TPP)





→ transketolase, dehydrogenase, decarboxylase

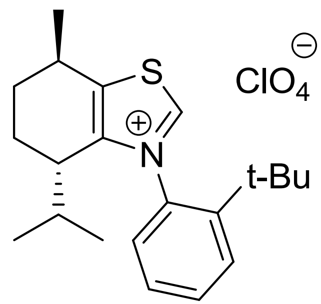
- Diseases: beriberi, Korsakoff's syndrome, optic neuropathy

Sundström, M.; Lindqvist, Y.; Schneider, G.; Hellman, U.; Ronne, H. *J. Biol. Chem*. **1993**, *268* (32), 24346-24352.
Jordan, F. *Nat. Prod. Rep.* **2003**, *20*, 171-183.

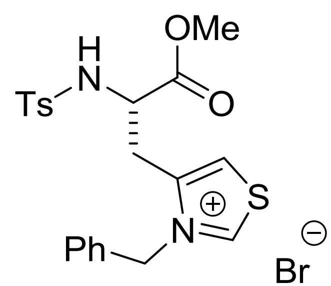
Appearance & relevance

Chemistry: Umpolung reactions, all kinds of Stetter reactions & benzoin-condensations, different applications in organocatalysis...

e.g., catalysts by **T. Bach**

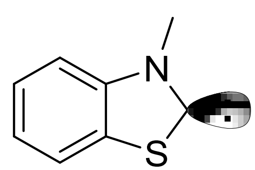


or **J. S. Miller**



- Development of other catalysts (e.g., **NHC**s) and their use in coordination chemistry

⟶ **Wanzlick**-inspired carbenes



Christmann, M. *Angew. Chem.* **2005**, *117*, 2688-2690. \ Wanzlick, H. W.; Schikora, E. A. *Angew. Chem.* **1960**, *72*, 494.

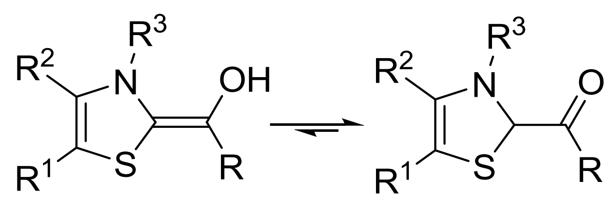
State of the art

"To our knowledge, there has been no unambiguous identification of the key intermediate in NHC umpolung catalysis, namely the Breslow intermediate."

(A. Berkessel, **2010**)

- **F. Jordan** *et al.* gained UV-absorbtions typical for an enaminol at around 380 nm

⟶ evidence for the Breslow intermediate ?



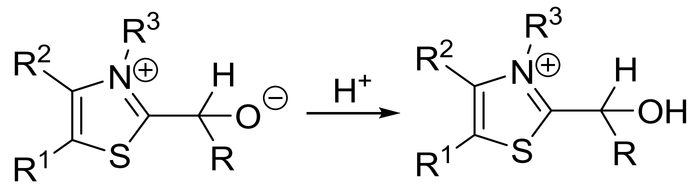
- DFT computations and further experiments with more stable derivates always point to the formation of the <u>keto-tautomer.</u>

- **Is it at all possible to detect the Breslow intermediate with spectroscopic methods ?**

Berkessel, A.; Elfert, S.; Etzenbach-Effers, K.; Teles, J. H. *Angew. Chem. Int. Ed*. **2010**, *49*, 7120-7124
Barletta, G.; Chung, A. C.; Rios, C. B.; Jordan, F.; Schlegel, J. *J. Am. Chem. Soc*. **1990**, *112*, 8144-8149.

State of the art

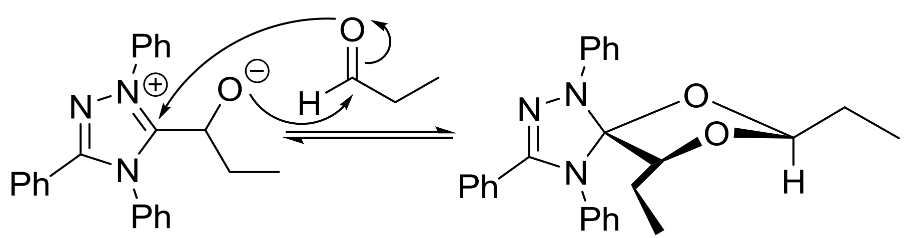
Other intermediates from the cycle



- NMR-studies of **R. Breslow** and **R. Kim** were able to prove the existence of 2-(α-hydroxymethyl)thiazolium

- Also identified by **W. Schrader** *via* mass measurements

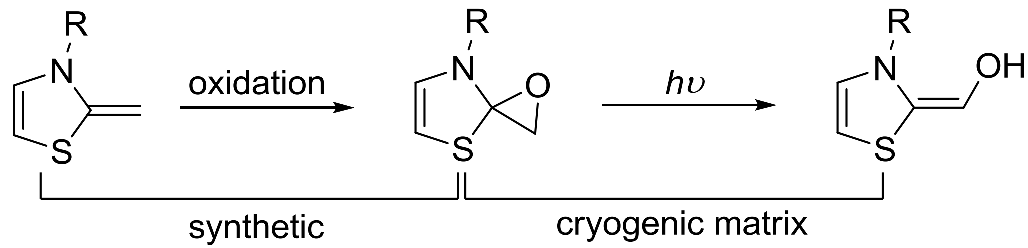
- The latest NMR studies performed by **A. Berkessel** and **J. H. Teles** point to another possible side reaction:



Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35* (5), 699-702.
Schrader, W.; Handayani, P. P.; Burstein; C.; Glorius, F. *Chem. Commun.* **2007**, *7*, 716-718.

Project aim

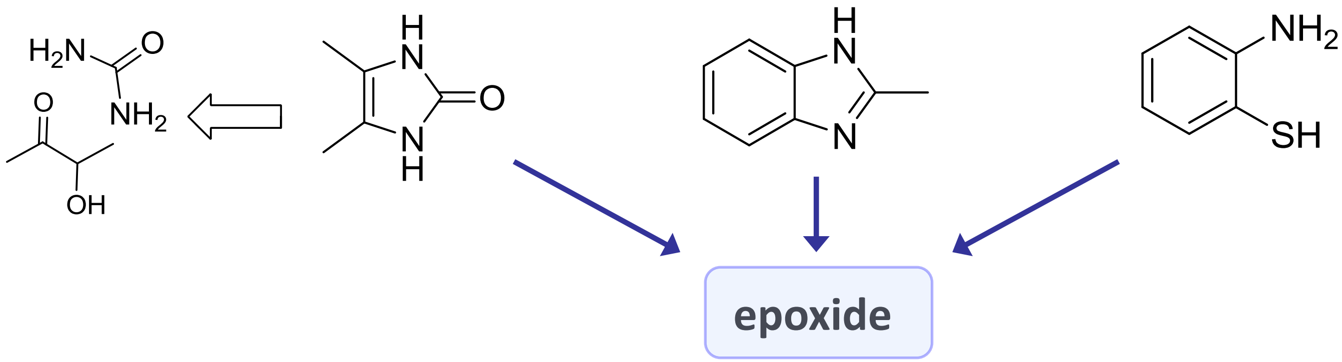
Two-part synthesis



advantage: ring-opening in a cryogenic matrix ⟶ no bimolecular side reactions

challenge: generation of an useful epoxide

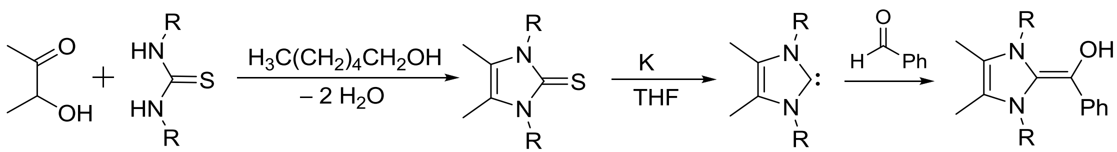
synthetic strategy **1.** **2.** **3.**

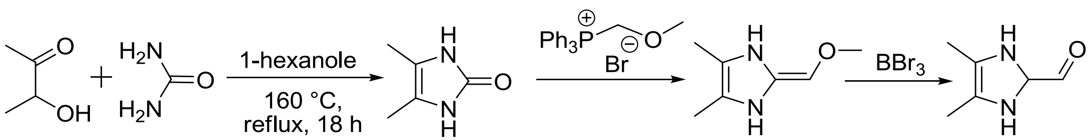


disadvantage: molecule must not be too bulky to allow transition into the gas phase

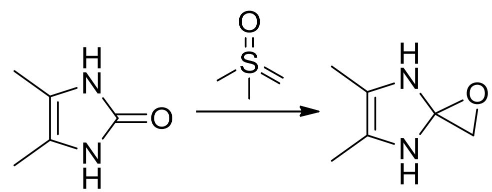
1. Imidazole route

- Synthesis by **N. Kuhn** & **T. Kratz**

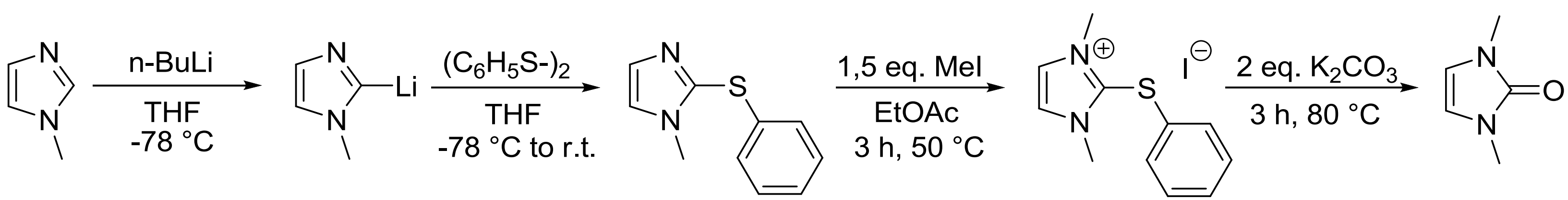




- Direct **Corey–Chaykovsky** epoxidation:



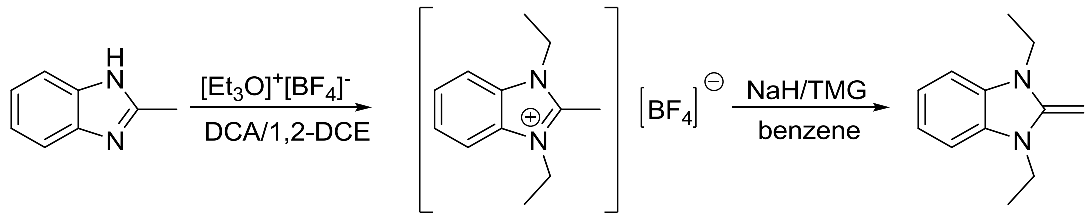
- Approach by **S. Ohishi**

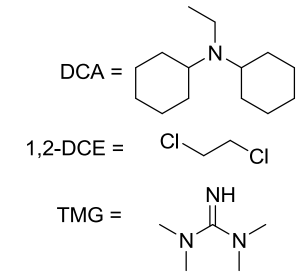


Kuhn, N.; Kratz, T. *Synthesis* **1993**, 561-562. \ Corey, E. J.; Chaykovsky, M. J. Am. Chem. Soc. **1965**, *87* (6), 1353-1364.
Nakamura, S.; Tsuno, N.; Yamashita, M.; Kawasaki, I.; Ohta, S.; Ohishi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 429-436.

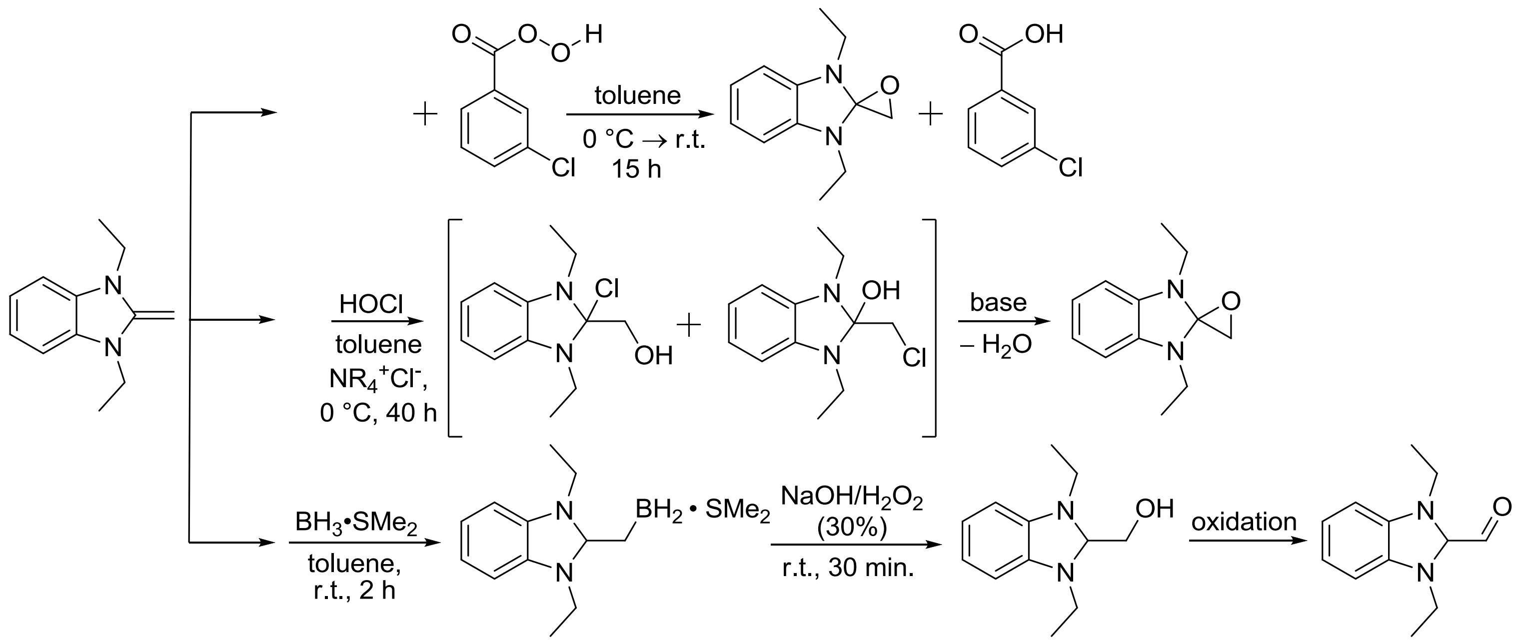
2. Benzimidazole route

- According to synthesis by **C. Reichardt** & **N. Kaufmann**





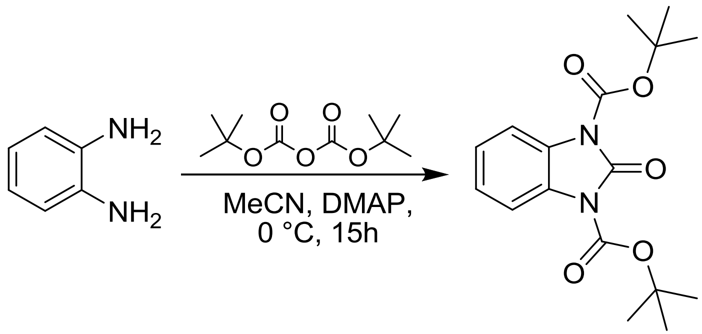
- Based on an exocyclic methylene moiety



Reichardt, C.; Kaufmann, N. *Chem Ber.* **1985**, *118*, 3424-3427.

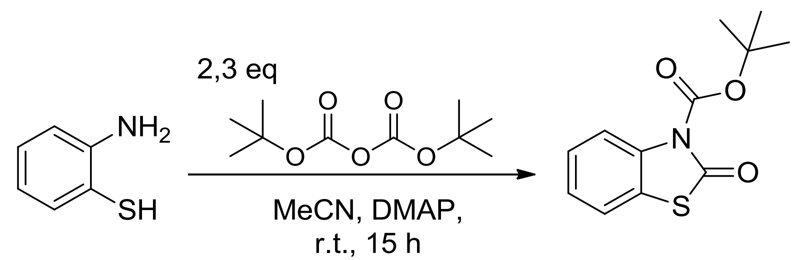
3. Aminothiophenol route

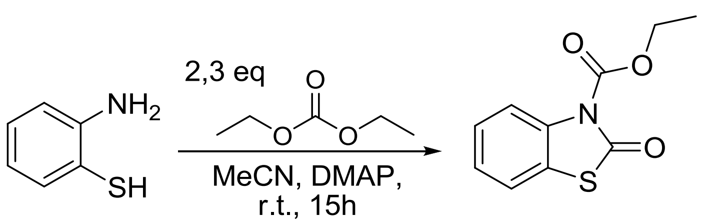
- Intramolecular cyclizations



- First cyclization with benzene-1,2-diamine

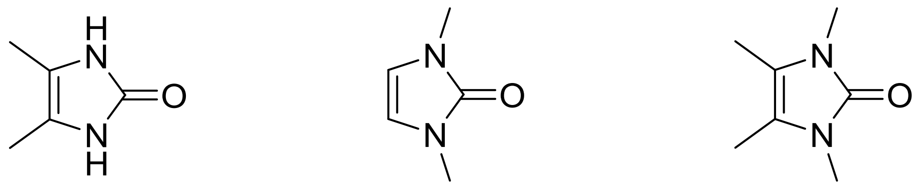
- Repeated with aminothiophenol





- Different cyclization agent

- Yields in the synthesis of:

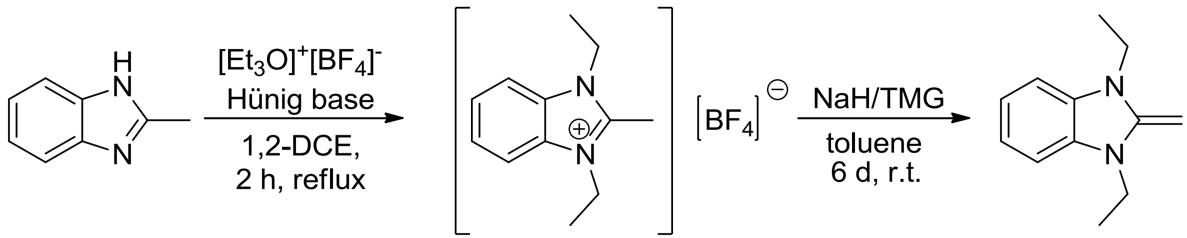


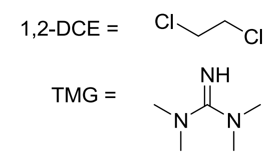
yield [%]: 16 % 11 % impure

- **No** detectable amounts of the epoxide

- Subsequent **Wittig** reaction has not yet been performed

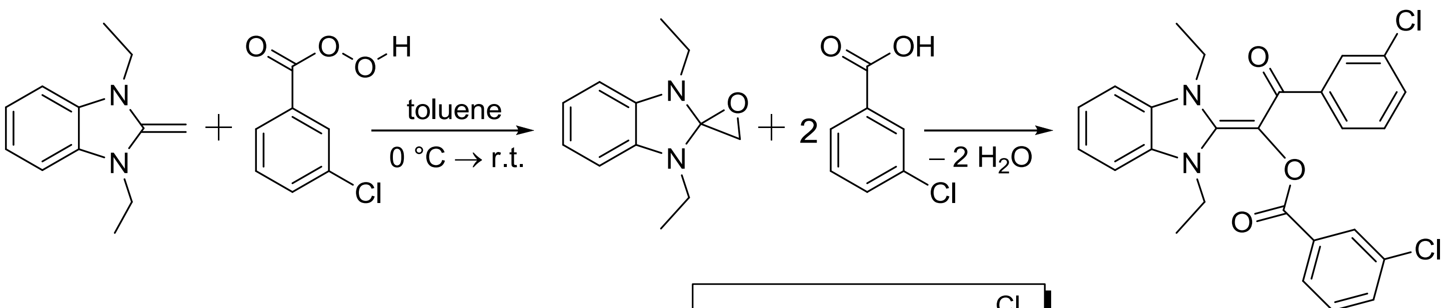
The **benzimidazole** route:

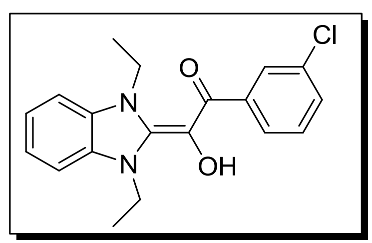




⟶ the product was kept in toluene and under inert gas

- **No** synthetic route has led to the desired epoxide yet, but:

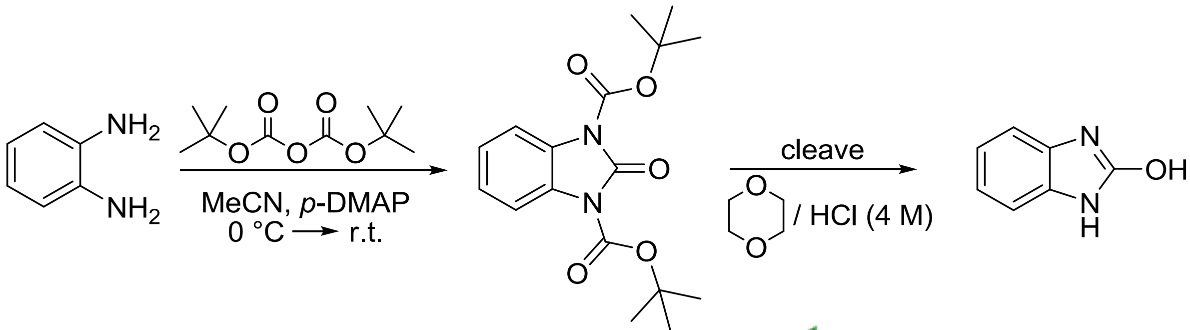


⟶ **[M+H]$^+$** 343.2 **M =** 

Reichardt, C.; Kaufmann, N. *Chem Ber.* **1985**, *118*, 3424-3427.

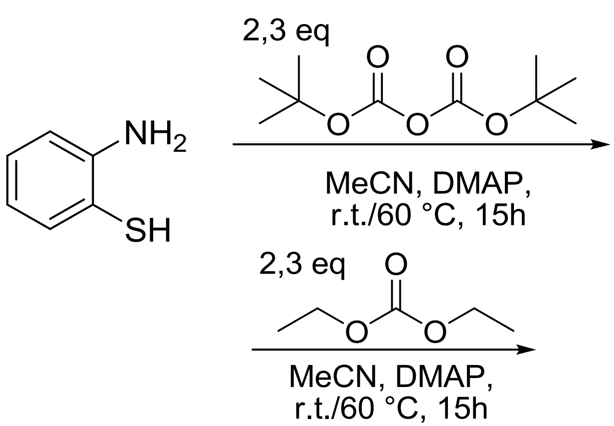
Results & discussion

- Results of the third route were surprising…

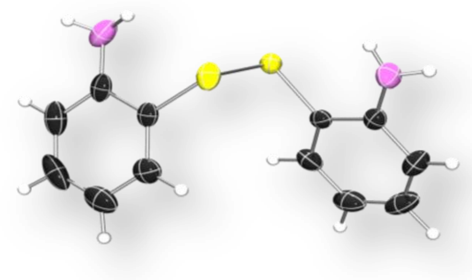


yield: 58 %

Aminothiophenol



? +

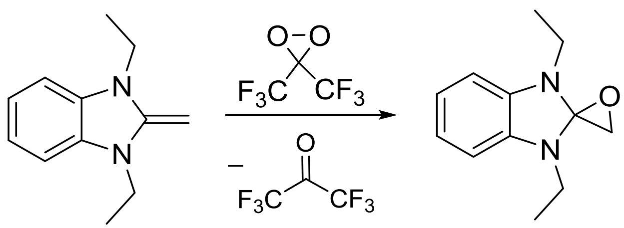


⟶ repeated with K_2CO_3

Outlook

Improvements for the present strategies

- Lower temperatures may lead to the desired intramolecular ring closure
- Conduct the epoxidation in a <u>buffered medium</u> or in <u>presence of a base</u> to avoid consecutive reactions
- Other epoxidation reagents

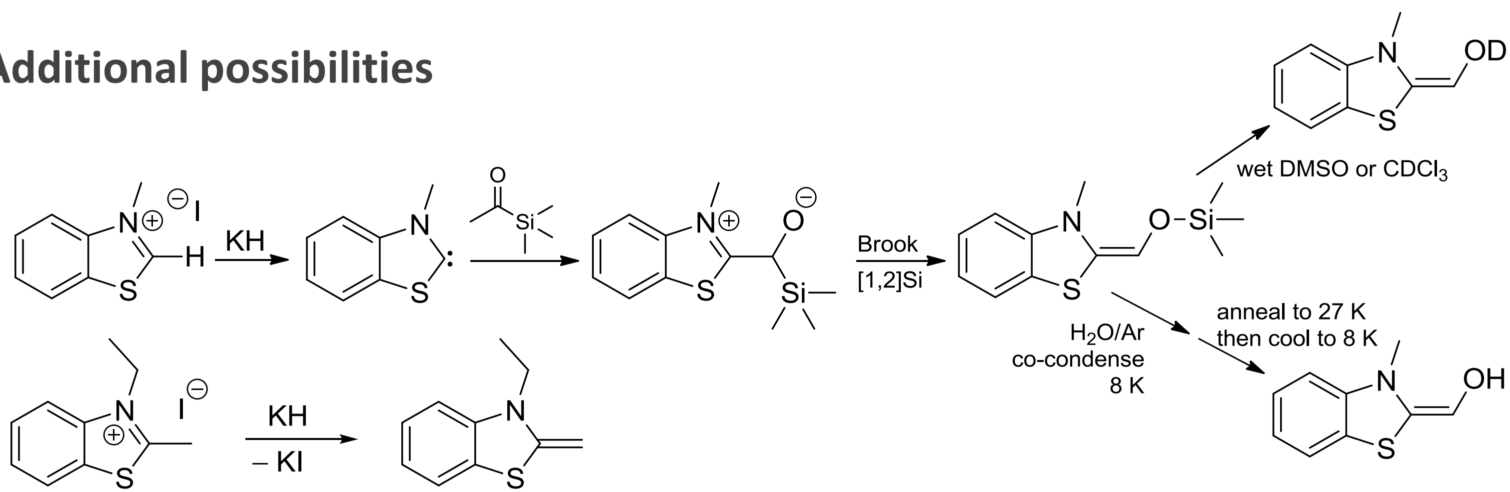


or

maybe with an **organic catalyst**, **imidoperacetic acid**, etc.

methylene substrate + $\mathbf{O_2}$ or $\mathbf{H_2O}$

Additional possibilities



Fürstner, A.; Alcarazo, M.; Goddard, R.; Lehmann, C. W. *Angew. Chem. Int. Ed*. **2008**, *47*, 3210-3214.

Vielen Dank,

Herrn Prof. Dr. Schreiner

&

der gesamten Arbeitsgruppe!

Besonders.........

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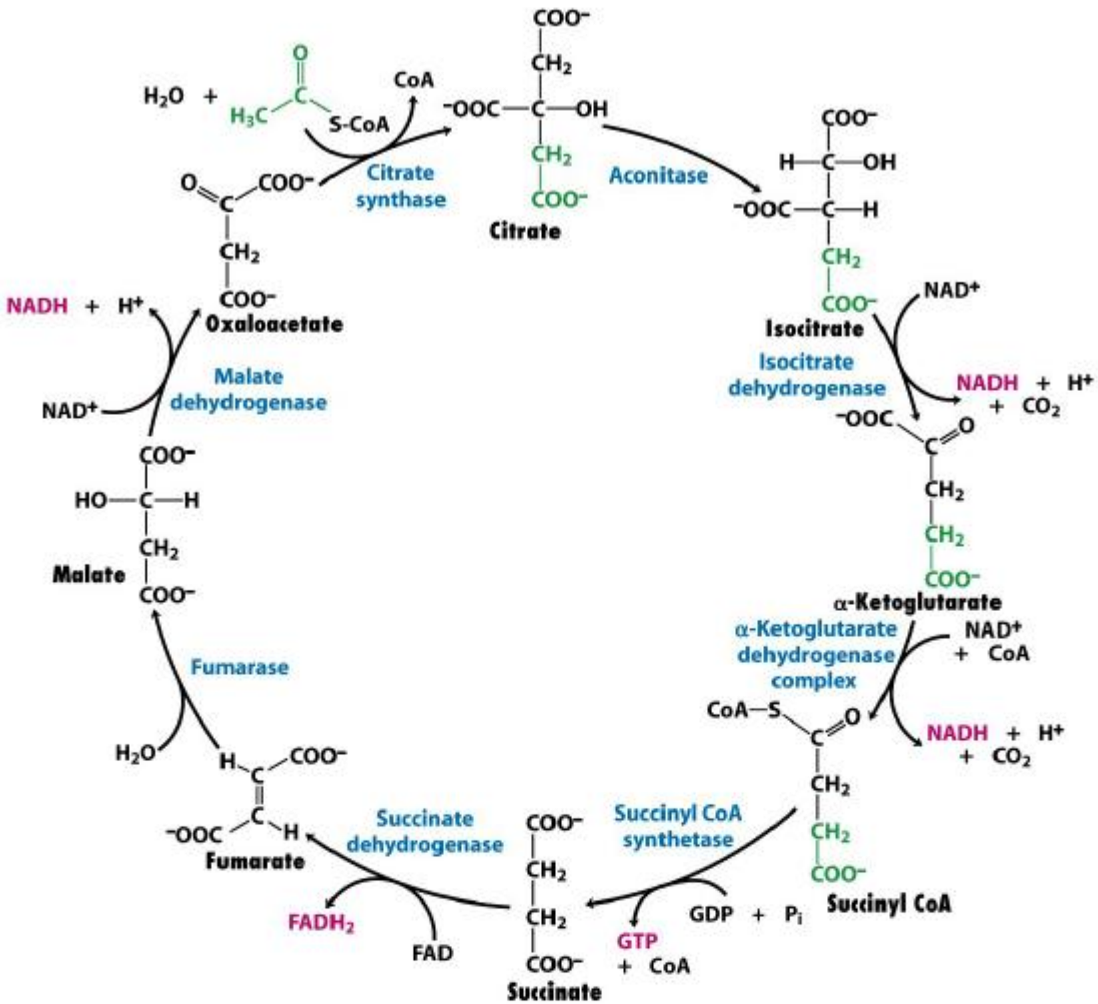
[a] http://www.columbia.edu/cu/chemistry/breslow/ 04/12/2012

Citric acid cycle

The citric acid cycle as a source of biosynthetic precursors: not only a catabolic, but also an anabolic function



Stryer, Biochemie, *6. Auflage*, **2007,** Elsevier GmbH, Spektrum, Heidelberg